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February 8, 1982

Professor Harold E. Varmus
Department of Microbiology & Immunology
University of California
San Francisco, CA 94143
U.S.A.

Dear Harold:

Thanks for your letter about the lambda phage libraries relating to the possibility of creating some such library from the F_1.

The whole idea is rather exciting to me: you remember I rather jokingly remarked that I supposed the only way we would ever really know if there were mutations in the children of the exposed would be to characterize the entire genome, which at this point in time seems like a very tall order indeed.

You pointed out that there were (at least as I understood it) many identical repeating sections of DNA throughout the genome, and it is certainly reasonable to assume that there must be random mutations in these otherwise silent sections. By 'silent' I guess we all mean the long stretches of DNA that don't get transcribed, or at least eventually do not code for any proteins that we know of, and have some other unknown (control) uses, right? If this sounds childish, lay it to my ignorance.

Thus, as I understood it in my all too brief talk with you, it would appear appropriate to try and identify mutations in these stretches of identical DNA, as a better approach than the "shot-gun" one we use now, identifying gene products of single genes, using methods that happen to be available.

Some questions intrude: first, I suppose that one may assume more or less random mutations, so that 'silent' or expressed genes alike would be affected; by the same token, what of polymorphisms in the silent part of the genome - what is the "noise" level, if, indeed it is known, and how to deal with it? If one had a probe for the repeating silent segments, one might have an enormous task in following up the presumed variants (by family studies). We have a large amount of work with our study as it is now, and one wonders if this would be greatly magnified?

As you can see, we are enormously intrigued. I talked this over briefly with Dr. Clifton, our Director of Research, who was equally fascinated. I really need to learn more about the possibilities and ways of searching for mutations in the human genome at this level before

I can even address the problem intelligently. Some of the geneticists are sceptical about this approach; we are having a meeting to decide the future of the genetics program here at the end of this month, and I would hope you might help me a bit with more details (or lead me to sources that will help me). Anyhow, the whole idea is certainly exciting!

Sincerely yours,

Howard B. Hamilton, M.D.
Chief, Clinical Laboratories

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